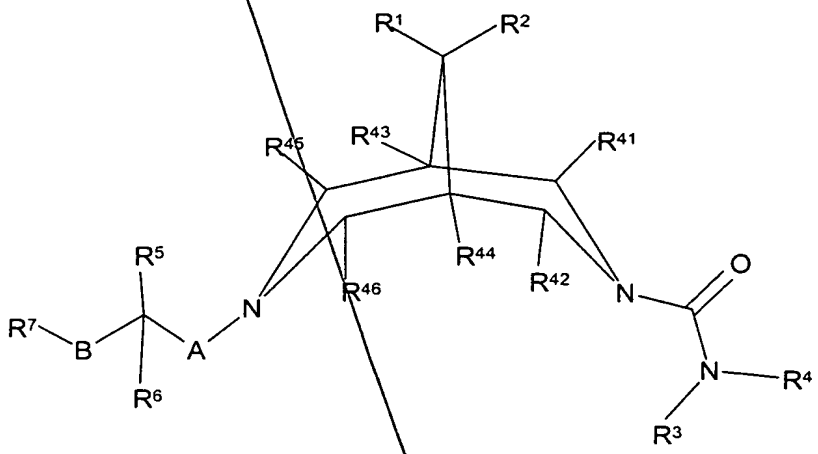
Claims

1. A compound of formula I,



I

wherein

R^1 and R^2 independently represent H, C_{1-4} alkyl, OR^{2b} or $N(R^{2c})R^{2d}$, or together form $-O-(CH_2)_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$;
R^{2b}, R^{2c} and R^{2d} independently represent H or C_{1-6} alkyl;

R^3 represents H, C_{1-6} alkyl or, together with R^4, represents C_{3-6} alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C_{1-3} alkyl groups);
R^4 represents H, C_{1-12} alkyl, C_{1-6} alkoxy (which latter two groups are both optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy), $-(CH_2)_q$-aryl, $-(CH_2)_q$-oxyaryl, $-(CH_2)_q$-Het^1 (which latter three groups are optionally substituted (at the $-(CH_2)_q-$ part and/or the aryl/Het^1 part) by one or more substituents selected from -OH, halo, cyano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, C_{1-6} alkyl and/or C_{1-6} alkoxy),

$-(CH_2)_qN(H)C(O)R^8$, $-(CH_2)_qS(O)_2R^8$, $-(CH_2)_qC(O)R^8$, $-(CH_2)_qC(O)OR^8$, $-(CH_2)_qC(O)N(R^9)R^8$ or, together with R^3, represents C_{3-6} alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C_{1-3} alkyl groups);

q represents 0, 1, 2, 3, 4, 5 or 6;

R^8 represents H, C_{1-6} alkyl, aryl (which latter group is optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, C_{1-6} alkyl and/or C_{1-6} alkoxy) or, together with R^9, represents C_{3-7} alkylene;

R^9 represents H, C_{1-4} alkyl or, together with R^8, represents C_{3-7} alkylene;

Het^1 represents a five to twelve-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R^{41}, R^{42}, R^{43}, R^{44}, R^{45} or R^{46} independently represent H or C_{1-3} alkyl;

R^5 represents H, halo, C_{1-3} alkyl, $-OR^{12}$, $-N(R^{13})R^{12}$ or, together with R^6, represents =O;

R^6 represents H, C_{1-4} alkyl or, together with R^5, represents =O;

R^{12} represents H, C_{1-6} alkyl, $-S(O)_2-C_{1-4}$-alkyl, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{15})R^{15a}$ or aryl (which latter group is optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, C_{1-6} alkyl and/or C_{1-6} alkoxy);

R^{13} represents H or C_{1-4} alkyl;

R^{14} represents H or C_{1-6} alkyl;

R^{15} and R^{15a} independently represent H or C_{1-4} alkyl, or together represent C_{3-6} alkylene, optionally interrupted by an O atom;

A represents a single bond, C_{1-6} alkylene, $-N(R^{16})(CH_2)_r-$ or $-O(CH_2)_r-$ (in which two latter groups, the $-(CH_2)_r-$ group is attached to the bispidine nitrogen atom);

B represents a single bond, C_{1-4} alkylene, $-(CH_2)_nN(R^{17})-$, $-(CH_2)_nS(O)_p-$, $-(CH_2)_nO-$ (in which three latter groups, the $-(CH_2)_n-$ group is attached to the carbon atom bearing R^5 and R^6), $-C(O)N(R^{17})-$ (in which latter group, the -C(O)- group is attached to the carbon atom bearing R^5 and R^6), $-N(R^{17})C(O)O(CH_2)_n-$, $-N(R^{17})(CH_2)_n-$ (in which two latter groups, the $N(R^{17})$ group is attached to the carbon atom bearing R^5 and R^6) or $-(CH_2)_mC(H)(OH)(CH_2)_n-$ (in which latter group, the $-(CH_2)_m-$ group is attached to the carbon atom bearing R^5 and R^6);

m represents 1, 2 or 3;

n and r independently represent 0, 1, 2, 3 or 4;

p represents 0, 1 or 2;

R^{16} and R^{17} independently represent H or C_{1-4} alkyl;

R^7 represents C_{1-6} alkyl, aryl or Het^2, all of which groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, Het^3, $-C(O)R^{10}$, $-C(O)OR^{11}$, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(H)S(O)_2R^{18}$, $-S(O)_2R^{19}$, $-OS(O)_2R^{20}$, $-N(H)C(O)N(H)R^{21}$, $-C(O)N(H)R^{22}$ and/or aryl (which latter group is optionally substituted by one or more cyano groups);

Het^2 and Het^3 independently represent a five to twelve-membered heterocyclic group containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R^{18}, R^{19} and R^{20} independently represent C_{1-6} alkyl;

R^{21} and R^{22} independently represent H or C_{1-6} alkyl (optionally terminated by cyano); and

R^{10} and R^{11} independently represent, at each individual occurrence, H or C_{1-6} alkyl;

R^{11a} represents, at each individual occurrence, C_{1-6} alkyl;

or a pharmaceutically acceptable derivative thereof;

provided that:

(a) when A and B are both single bonds and R^7 is optionally substituted aryl, then R^5 and R^6 do not both represent H;

(b) when A represents a single bond, then R^5 and R^6 do not together represent =O; and

(c) when R^5 represents $-OR^{12}$ or $-N(R^{13})R^{12}$, then:-

(i) A does not represent $-N(R^{16})(CH_2)_r-$ or $-O(CH_2)_r-$; and/or

(ii) n does not represent 0 when B represents $-(CH_2)_nN(R^{17})-$, $-(CH_2)_nS(O)_p-$ or $-(CH_2)_nO-$.

2. A compound as claimed in Claim 1, wherein R^1 represents H.

3. A compound as claimed in Claim 1 ~~or Claim 2~~, wherein R^2 represents H.

4. A compound as claimed in Claim 1 ~~any one of the preceding claims~~, wherein R^3 represents H; C_{1-2} alkyl; or, together with R^4 represents C_{4-5} alkylene, optionally interrupted by an O atom and/or optionally substituted by one or more methyl groups.

5. A compound as claimed in Claim 4, wherein R^3 represents H.

110 claim 1

6. A compound as claimed in ~~any one of the preceding claims~~, wherein R^4 represents H; linear or branched and/or saturated or unsaturated and/or cyclic, acyclic and/or part cyclic/acyclic C_{1-8} alkyl (which alkyl group is optionally substituted by one or more cyano or halo groups and/or interrupted by an O atom); C_{1-6} alkoxy; $-(CH_2)_qS(O)_2R^8$, $-(CH_2)_qC(O)OR^8$, $-(CH_2)_qN(H)C(O)R^8$, $-(CH_2)_qC(O)R^8$, (in which latter four groups, q represents 0, 1 or 2 and R^8 represents linear or branched and/or acyclic, cyclic and/or part cyclic/acyclic C_{1-4} alkyl, or phenyl (which phenyl group is optionally substituted by one or more cyano and/or C_{1-3} alkyl groups)); $-(CH_2)_qC(O)N(R^9)R^8$ (in which latter group, q represents 0, 1 or 2 and R^8 and R^9 independently represent H, linear or branched and/or acyclic, cyclic and/or part cyclic/acyclic C_{1-4} alkyl, or together represent C_{4-6} alkylene); $-(CH_2)_q$-phenyl, $-(CH_2)_q$-oxyphenyl or $-(CH_2)_q$-Het^1 (in which latter three groups, q represents 0, 1, 2 or 3, the $-(CH_2)_q-$ part is optionally substituted by a cyano group, and the phenyl, or Het^1, part is optionally substituted with one or more substituents selected from cyano, nitro, linear or branched C_{1-4} alkyl, linear or branched C_{1-4} alkoxy and $N(H)S(O)_2R^{11a}$); or, together with R^3, represents C_{4-5} alkylene, optionally interrupted by an O atom and/or optionally substituted by one or more methyl groups.

claim 1

7. A compound as claimed in ~~any one of the preceding claims~~, wherein R^5 represents H; fluoro; OR^{12} (in which R^{12} represents H, phenyl (optionally substituted by one or more methoxy groups) or $C(O)N(H)R^{15a}$ (in which R^{15a} represents linear or branched C_{1-4} alkyl)); $-N(R^{13})(R^{12})$ (in which R^{12} represents H, C_{1-2} alkyl, $-S(O)_2$-C_{1-2} alkyl, $-C(O)R^{14}$ (in which R^{14} represents C_{1-2} alkyl), $-C(O)OR^{14}$ (in which R^{14} represents linear or branched C_{1-5} alkyl) or $-C(O)N(R^{15})(R^{15a})$ (in which R^{15} and R^{15a} independently represent H or linear or branched C_{1-3} alkyl or together represent C_{4-5} alkylene, which

alkylene group is optionally interrupted by an O atom) and R^{13} represents H or C_{1-2} alkyl); or, together with R^6, represents =O.

8. A compound as claimed in Claim 7, wherein R^5 represents H, OH or $-N(H)C(O)N(R^{15})(R^{15a})$.

9. A compound as claimed in ~~any one of the preceding claims,~~ claim 1 wherein R^6 represents H or C_{1-2} alkyl or together with R^5 represents =O.

10. A compound as claimed in Claim 9, wherein R^6 represents H.

11. A compound as claimed in ~~any one of the preceding claims~~ claim 1, wherein A represents a single bond, linear or branched C_{1-4} alkylene (which group is also optionally interrupted by O), $-N(H)(CH_2)_r-$ or $-O(CH_2)_r-$ (in which latter two cases r is 1 or 2).

12. A compound as claimed in Claim 11, wherein A represents $-CH_2-$ or $-(CH_2)_2-$.

13. A compound as claimed in ~~any one of the preceding claims~~ claim 1, wherein B represents a single bond, C_{1-4} alkylene, $-(CH_2)_nO-$, $-(CH_2)_nS(O)_2-$, $-(CH_2)_nN(H)-$ or $-N(H)(CH_2)_n-$ (in which latter four cases n is 0, 1, 2 or 3).

14. A compound as claimed in Claim 13, wherein B represents a single bond, $-CH_2N(H)-$ or $-CH_2O-$.

15. A compound as claimed in ~~any one of the preceding claims~~ claim 1, wherein R^7 represents linear or branched and/or acyclic, cyclic and/or part cyclic/acyclic C_{1-6} alkyl (optionally substituted and/or terminated by OH);

Het^2 (optionally substituted by one or more substituents selected from cyano, C_{1-3} alkyl, phenyl (which latter group is optionally substituted with one or more cyano groups), =O, $C(O)R^{10}$ (in which R^{10} is linear or branched C_{1-3} alkyl) or $S(O)_2R^{19}$ (in which R^{19} is C_{1-2} alkyl)); or phenyl (optionally substituted by one or more substituents selected from cyano, nitro, linear or branched C_{1-3} alkyl, linear or branched C_{1-3} alkoxy, fluoro, chloro, $C(O)N(H)R^{22}$ (in which R^{22} represents linear or branched and/or acyclic, cyclic and/or part cyclic/acyclic C_{1-4} alkyl, which alkyl group is optionally terminated by cyano), $N(H)S(O)_2R^{18}$ (in which R^{18} represents C_{1-2} alkyl) or Het^3).

16. A compound as claimed in Claim 15, wherein R^7 represents phenyl (substituted by a cyano group (preferably in the 4-position relative to B) and by one or more optional $C(O)N(H)R^{22}$ substituent).

17. A compound as claimed in ~~any one of the preceding claims~~, wherein R^{41}, R^{42}, R^{43}, R^{44}, R^{45} and R^{46} all represent H.

18. A pharmaceutical formulation including a compound as defined in ~~any one of Claims 1 to 17~~ in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

19. A pharmaceutical formulation for use in the prophylaxis or the treatment of an arrhythmia, comprising a compound as defined in ~~any one of Claims 1 to 17~~.

20. A compound as defined in ~~any one of Claims 1 to 17~~ for use as a pharmaceutical.

21. A compound as defined in ~~any one of Claims 1 to 17~~ Claim 1 for use in the prophylaxis or the treatment of an arrhythmia.

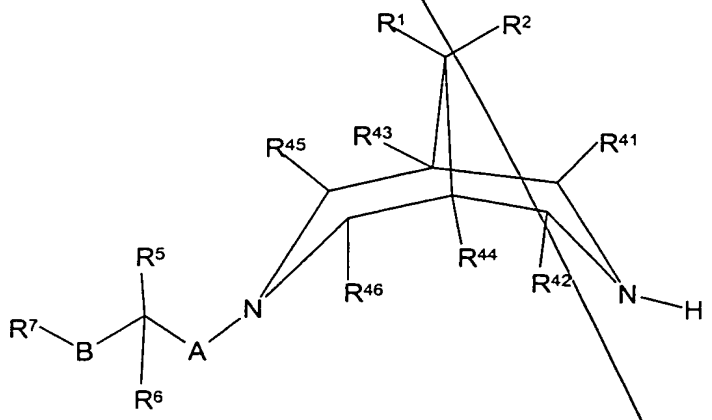
22. The use of a compound as defined in ~~any of one Claims 1 to 17~~ Claim 1 as active ingredient in the manufacture of a medicament for use in the prophylaxis or the treatment of an arrhythmia.

23. The use as claimed in Claim 22, wherein the arrhythmia is an atrial or a ventricular arrhythmia.

24. A method of prophylaxis or treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound as defined in ~~any one of Claims 1 to 17~~ Claim 1 to a person suffering from, or susceptible to, such a condition.

25. A process for the preparation of a compound of formula I as defined in Claim 1 which comprises:

(a) for compounds of formula I in which R^3 is H, reaction of a compound of formula II,



II

wherein R^1, R^2, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1 with a compound of formula III,

$$R^4\text{-}N{=}C{=}O \qquad \text{III}$$

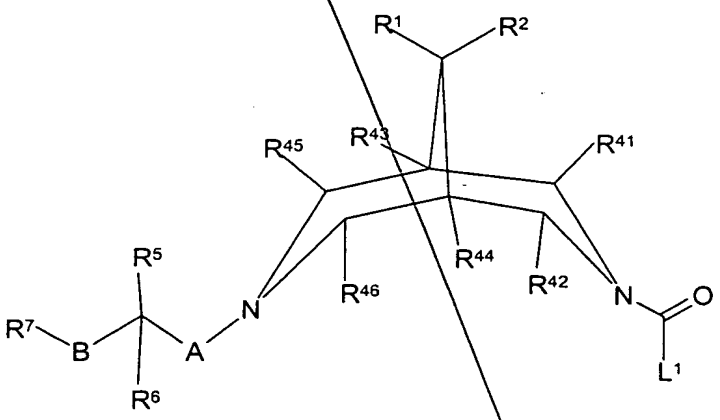
wherein R^4 is as defined in Claim 1;

(b) reaction of a compound of formula II, as defined above, with a carbonic acid derivative of formula IV,

$$(R^3)(R^4)NC(O)\text{-}L^1 \qquad \text{IV}$$

wherein L^1 represents a leaving group and R^3 and R^4 are as defined in Claim 1;

(c) reaction of a compound of formula V,



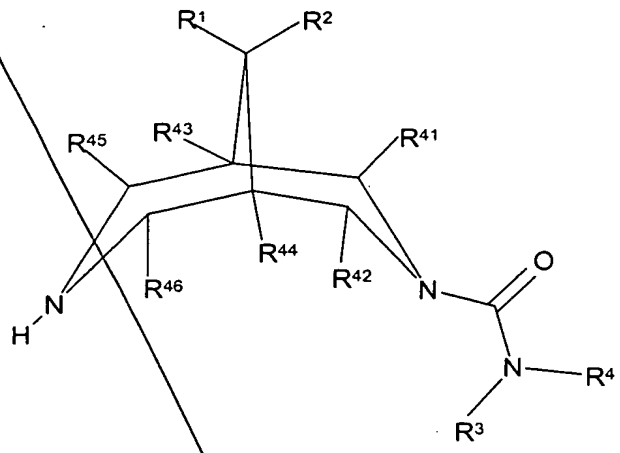
V

wherein and L^1 is as defined above and R^1, R^2, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1, with a compound of formula VA,

$$(R^3)(R^4)NH \qquad \text{VA}$$

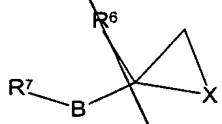
wherein R^3 and R^4 are as defined in Claim 1;

(d) for compounds of formula I in which A represents CH_2 and R^5 represents -OH or $-N(H)R^{12}$, reaction of a compound of formula VI,



VI

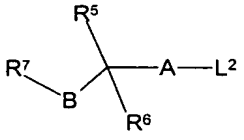
wherein R^1, R^2, R^3, R^4, R^{41}, R^{42}, R^{43}, R^{44}, R^{45} and R^{46} are as defined in Claim 1, with a compound of formula VII,



VII

wherein X represents O or $N(R^{12})$ and R^6, R^7, R^{12} and B are as defined in Claim 1;

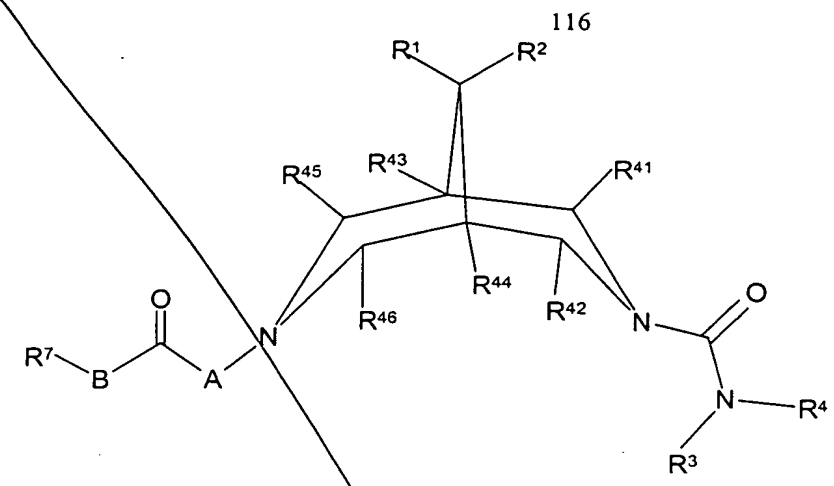
(e) reaction of a compound of formula VI, as defined above, with a compound of formula VIII,



VIII

wherein L^2 represents a leaving group and R^5, R^6, R^7, A and B are as defined in Claim 1;

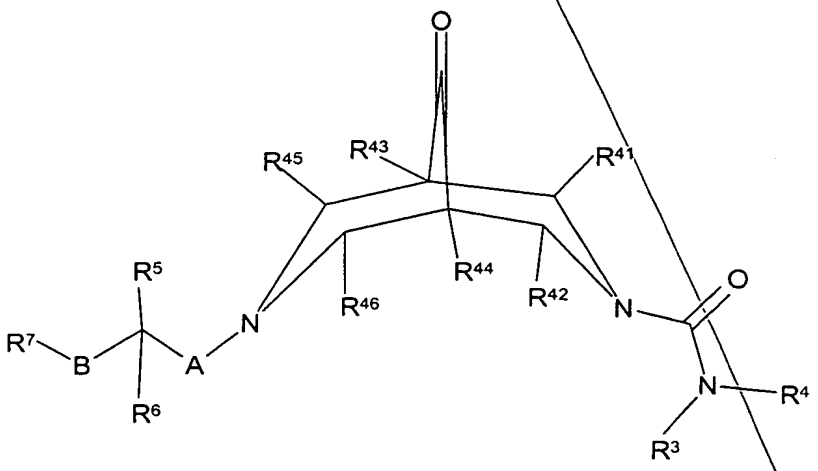
(f) for compounds of formula I in which R^5 represents H or OH and R^6 represents H, reduction of a compound of formula IX,



IX

wherein R^1, R^2, R^3, R^4, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1;

(g) for compounds of formula I in which one of R^1 and R^2 represents H or OH and the other represents H, reduction of a corresponding compound of formula X,

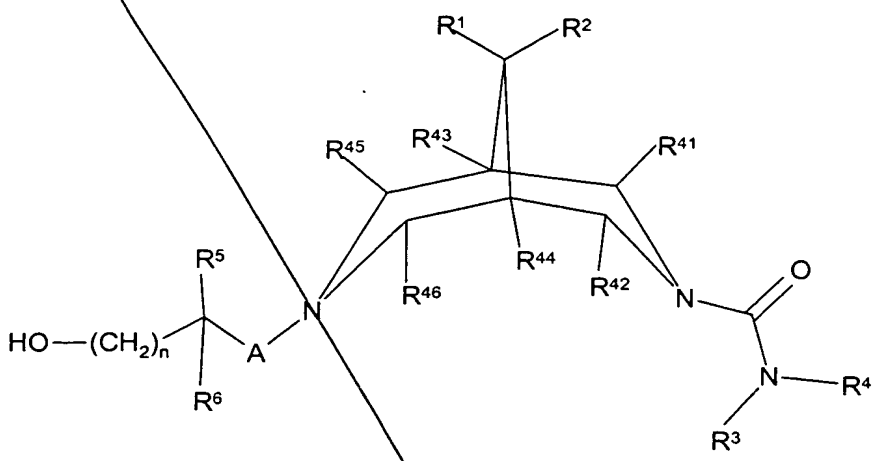


X

wherein R^3, R^4, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1;

(h) for compounds of formula I in which R^1 and R^2 together represent $-O(CH_2)_2O-$, reaction of a corresponding compound of formula X as defined above with ethane-1,2-diol;

(i) for compounds of formula I in which B represents $-(CH_2)_nO-$, reaction of a compound of formula XI,



XI

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and n are as defined in Claim 1, with a compound of formula XIA,

$$R^7OH \qquad \text{XIA}$$

in which R^7 is as defined in Claim 1;

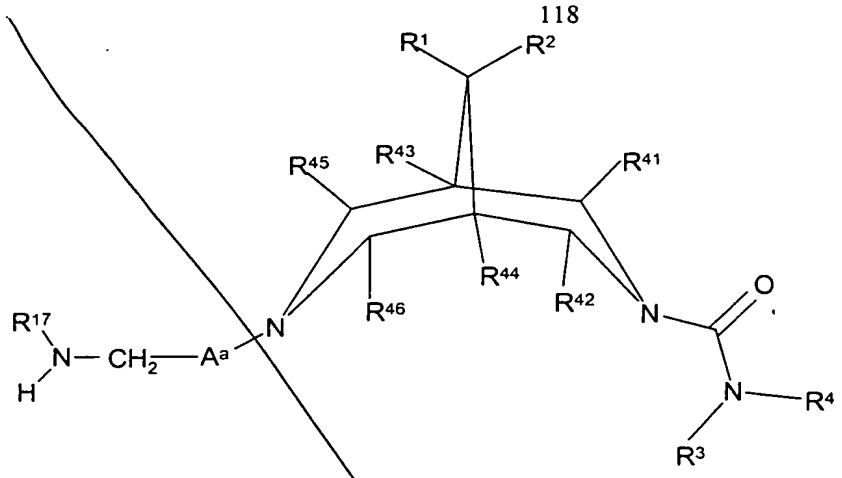
(j) for compounds of formula I which are bispidine-nitrogen N-oxide derivatives, oxidation of the corresponding bispidine nitrogen of a corresponding compound of formula I;

(k) for compounds of formula I which are C_{1-4} alkyl quaternary ammonium salt derivatives, in which the alkyl group is attached to a bispidine nitrogen, reaction, at the bispidine nitrogen, of a corresponding compound of formula I with a compound of formula XII,

$$R^bL^3 \qquad \text{XII}$$

wherein R^b represents C_{1-4} alkyl and L^3 is a leaving group;

(l) for compounds of formula I in which R^5 and R^6 represent H, A represents C_{1-6} alkylene and B represents $-N(R^{17})(CH_2)_n-$, reaction of a compound of formula XIII,



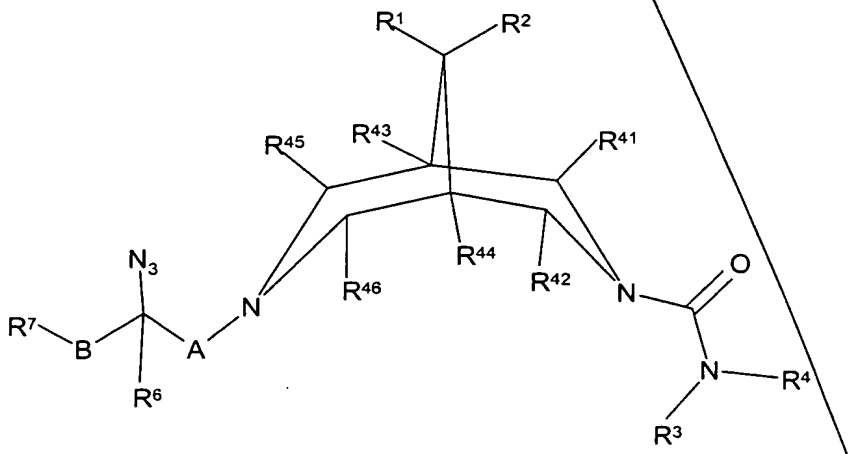
XIII

wherein A^a represents C_{1-6} alkylene and R^1, R^2, R^3, R^4, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46} and R^{17} are as defined in Claim 1 with a compound of formula XIV,

$$R^7\text{-}(CH_2)_n\text{-}L^2 \qquad \text{XIV}$$

wherein L^2 is as defined above and R^7 and n are as defined in Claim 1;

(m) for compounds of formula I in which R^5 represents $-NH_2$, reduction of a corresponding compound of formula XV,



XV

wherein R^1, R^2, R^3, R^4, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1;

(n) for compounds of formula I in which R^5 represents $-N(R^{13})C(O)NH(R^{15})$, reaction of a corresponding compound of formula I in which R^5 represents $-N(R^{13})H$ with a compound of formula XVI,

$$R^{15}N=C=O \qquad \text{XVI}$$

wherein R^{15} is as defined in Claim 1;

(o) for compounds of formula I in which R^5 represents $-N(R^{13})C(O)R^{14}$, reaction of a corresponding compound of formula I in which R^5 represents $-N(R^{13})H$ with a compound of formula XVII,

$$R^{14}C(O)R^x \qquad \text{XVII}$$

wherein R^x represents a suitable leaving group and R^{14} is as defined in Claim 1;

(p) for compounds of formula I in which R^5 represents $-N(H)R^{12}$, wherein R^{12} is as defined in Claim 1 provided that it does not represent H, reaction of a corresponding compound of formula I, in which R^5 represents $-NH_2$ with a compound of formula XVIII,

$$R^{12a}L^1 \qquad \text{XVIII}$$

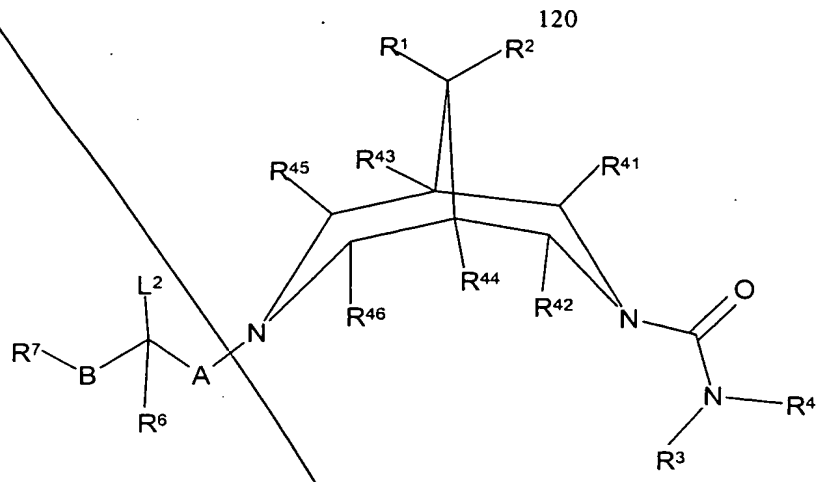
wherein R^{12a} represents R^{12} as defined in Claim 1 provided that it does not represent H and L^1 is as defined above;

(q) for compounds of formula I in which R^5 represents $-OR^{12}$ in which R^{12} represents C_{1-6} alkyl or optionally substituted aryl, reaction of a corresponding compound of formula I in which R^5 represents -OH with a compound of formula XIX,

$$R^{12a}OH \qquad \text{XIX}$$

wherein R^{12a} represents C_{1-6} alkyl or optionally substituted aryl;

(r) for compounds of formula I in which R^5 represents $-OR^{12}$, in which R^{12} represents C_{1-6} alkyl or optionally substituted aryl, reaction of a compound of formula XX,



XX

wherein L^2 is as defined above and R^1, R^2, R^3, R^4, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1 with a compound of formula XIX as defined above;

(s) for compounds of formula I in which R^5 represents OR^{12} and R^{12} represents $C(O)R^{14}$, reaction of a corresponding compound of formula I in which R^5 represents OH with a compound of formula XXI,

$$R^{14}CO_2H \qquad \text{XXI}$$

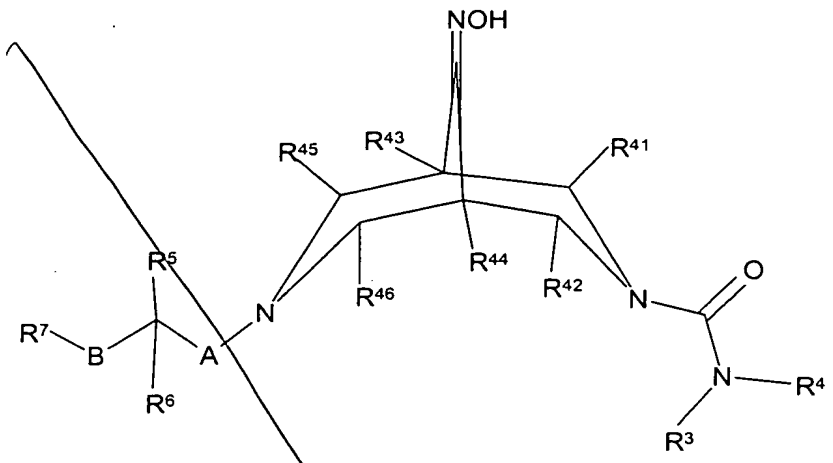
wherein R^{14} is as defined in Claim 1;

(t) for compounds of formula I in which R^5 represents halo, substitution of a corresponding compound of formula I in which R^5 represents -OH, using an appropriate halogenating agent;

(u) for compounds of formula I in which R^3 and/or R^4 as appropriate represent alkyl groups, alkylation of a corresponding compound of formula I, in which R^3 and/or R^4 (as appropriate) represent H;

(v) conversion of one R^4 group to another;

(w) for compounds of formula I in which one of R^2 and R^3 represents $-NH_2$ and the other represents H, reduction of a compound of formula XXIA,



XXIA

Sub C2

wherein R^3, R^4, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1;

(x) for compounds of formula I in which one or both of R^1 and R^2 represent $-N(R^{2c})R^{2d}$ in which one or both of R^{2c} and R^{2d} represents C_{1-6} alkyl, alkylation of a corresponding compound of formula I in which R^1 and/or R^2 represent $-N(R^{2c})R^{2d}$ (as appropriate) in which R^{2c} and/or R^{2d} (as appropriate) represent H, using a compound of formula XXIB,

$$R^{2e}L^1 \qquad \text{XXIB}$$

wherein R^{2e} represents C_{1-6} alkyl and L^1 is as defined above;

(y) conversion of one substituent on R^7 to another; or

(z) deprotection of a protected derivative of a compound of formula I as defined in Claim 1.

Sub B5

26. A compound of formula II, as defined in Claim 25, or a protected derivative thereof, provided that R^7 does not represent optionally substituted phenyl.

27. A compound of formula V, as defined in Claim 25, or a protected derivative thereof, provided that R^7 does not represent optionally substituted phenyl.

28. A compound of formula X as defined in Claim 25, or a protected derivative thereof.

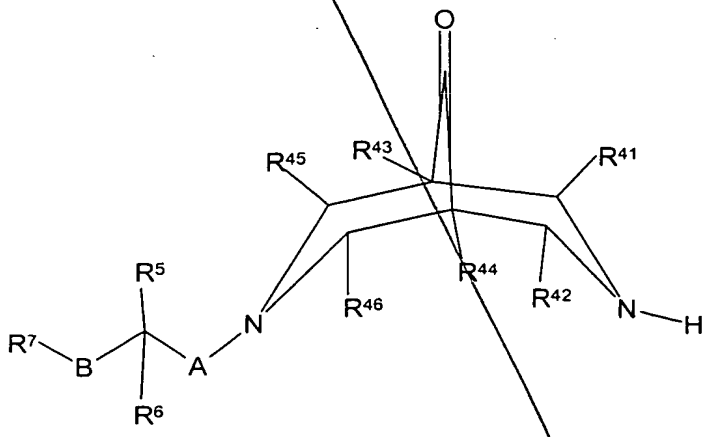
29. A compound of formula XI as defined in Claim 25, or a protected derivative thereof.

30. A compound of formula XIII, as defined in Claim 25, or a protected derivative thereof.

31. A compound of formula XV, as defined in Claim 25, or a protected derivative thereof.

32. A compound of formula XX, as defined in Claim 25, or a protected derivative thereof.

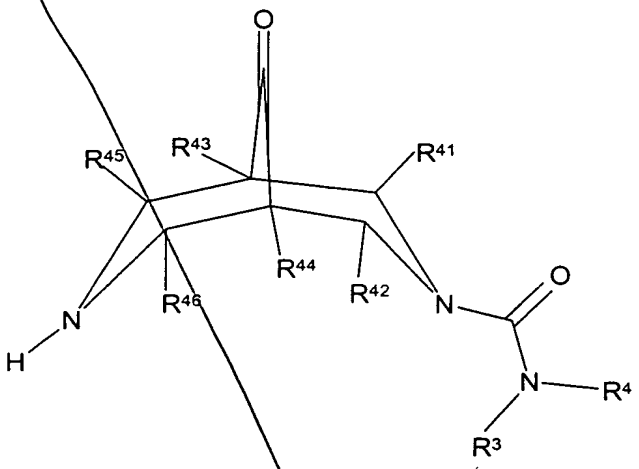
33. A compound of formula XXIII,



XXIII

wherein R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1, or a protected derivative thereof.

34. A compound of formula XXV,

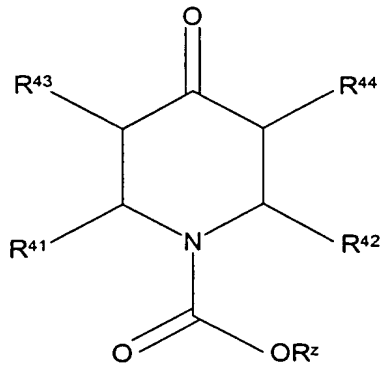


XXV

wherein R^3, R^4, R^{41}, R^{42}, R^{43}, R^{44}, R^{45} and R^{46} are as defined in Claim 1, or a protected derivative thereof.

35. A process for the preparation of a compound of formula X, of formula XXIII, or of formula XXV (in which, in all cases, R^{45} and R^{46} both represent H), which comprises (as appropriate) reaction of either:

(i) a compound of formula XXXV,



XXXV

wherein R^z represents C_{1-10} alkyl or C_{1-3} alkylaryl and R^{41}, R^{42}, R^{43} and R^{44} are as defined in Claim 1, or

(ii) 4-piperidone (or a protected derivative thereof),

with (as appropriate) either:

(1) a compound of formula XXXVI,

$$R^7\text{-B-C}(R^5)(R^6)\text{-A-NH}_2 \qquad \text{XXXVI}$$

wherein R^5, R^6, R^7, A and B are as defined in Claim 1, or

(2) NH_3 (or a protected derivative thereof),

in all cases in the presence of a formaldehyde and, in the case of compounds of formulae X and XXV, followed by conversion of the $C(O)OR^z$ group in the resultant intermediate to a $C(O)N(R^3)(R^4)$ group.

36. A process as claimed in Claim 35, in which the reaction is carried out in the presence of an organic acid.

37. A process as claimed in Claim 36, in which the organic acid is acetic acid.